Original Article

Age-related changes in macular vessels and their perfusion densities on optical coherence tomography angiography

Amar Pujari, Rohan Chawla, Ashish Markan, Pooja Shah, Suneel Kumar, Nasiq Hasan, Anu Sharma, Atul Kumar

Purpose: To evaluate age-related changes in macular vessels and their perfusion densities using optical coherence tomography angiography (OCTA). **Methods:** A total of 108 eyes of 54 healthy subjects between the age group of 11 to 60 years having unaided visual acuity of 20/20 were studied on spectral domain OCTS using 3 * 3 mm macula protocol. These subjects were divided into 5 groups; Group 1: 11–20 years, Group 2: 21–30 years, Group 3: 31–40 years, Group 4: 41–50 years, and Group 5: 51–60 years. An early treatment diabetic retinopathy study (ETDRS) grid overlay at the macula was used to calculate changes in different quadrants of the superficial retinal plexus. **Results:** A total of 98 eyes of 49 patients were considered for the final analysis. The vessel density values decreased from the second to the sixth decade in all four quadrants (except the third decade, where a slight increase was noted). The total vessel density decreased from 168 ± 78 mm^{-1} (group 1) to 131.47 ± 18.32 mm^{-1} (group 5). A similar reduction pattern in perfusion density was seen in each quadrant from the second to the sixth decade. The total perfusion density reduced from 309 ± 15.63% (group 1) to 283.05 ± 45.23% (group 5). The foveal avascular zone area was 0.18 ± 0.09 mm^2 in group 1, 0.33 ± 0.13 mm^2 in group 2, 0.30 ± 0.10 mm^2 in group 3, 0.38 ± 0.05 mm^2 in group 4, and 0.46 ± 0.06 mm^2 in group 5. **Conclusion:** In our population, macular vessel density appears to decrease noticeably from the fourth decade onwards but a statistically significant decrease was observed only from the fifth decade onwards. However, it was not uniform along with all the quadrants. Similarly, the percentage of perfusion density dropped from the fourth decade but these values also varied among the different quadrants.

Key words: Age-related macular vessel density changes, flow densities, Optical coherence tomography angiography

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Optical coherence tomography angiography (OCTA) is a noninvasive, retino-choroidal imaging technique with the ability to map the vasculature at different depths of retina and choroid. Therefore, diseases affecting the retinal or choroidal vasculature such as diabetic retinopathy and age-related macular degeneration can now be better understood *in vivo* at a micro-level. To understand the pathologies of various diseases, it is important to have normative data and to study their variation with age.[1-4] Present generation OCTA machines have inbuilt software, which can provide quantitative data regarding vessel densities (VDs) and perfusion densities (PDs) along with different retinal plexuses. The purpose of this study is to assess the age-related changes in superficial retinal plexus in terms of its VDs and PDs in the normal Indian population so as to facilitate future studies using OCTA.

Methods

Patients, present to our outpatient services (tertiary eye hospital in north India), underwent a detailed ocular examination as per our hospital protocols. Subjects with an unaided visual acuity of 20/20 in both the eyes and no history of previous ocular diseases/surgeries (significant ocular diseases including high refractive errors) or systemic pathologies (diabetes mellitus, hypertension, coronary artery disease, stroke, hypercholesterolemia, and others) were included in the observation. In addition, subjects with a history of smoking, use of vasodilating/vasoconstricting drugs, and any amount of refractive errors were excluded from the study. Subjects <10 years of age and >60 years of age were excluded because of the difficulty in scan acquisition in younger subjects, and a higher likelihood of medical or surgical interventions (usually cataract surgery) in the older population. This was a prospective observational study and this study adhered to the Declaration of Helsinki; each patient was explained about the procedure and written consent was obtained from each patient prior to examination. A total of 108 eyes (54 patients) were screened, of which 5 patients were excluded because of the poor-quality scans. A total of 98 eyes of 49 patients were included in the final observation and these were categorized into 5 groups (1 to 5) with respect to each decade (second to sixth decade). Each group consisted of 20 eyes except for group 5 which had 18 eyes.

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All subjects underwent macular OCTA on Zeiss Angioplex OCT, Carl Zeiss AG, Jena. A 3*3 mm scanning protocol was followed to acquire macular images. All scans were performed by a single observer; scans with signal strength/score >7 were considered satisfactory and included for final observation. The density and perfusion values were assessed using in-built OCTA software provided by the manufacturers. An ETDRS chart overlay was used to calculate perfusion density (PD) and vessel density (VD) in all quadrants around the fovea. The values along the superior, inferior, temporal, and nasal quadrants were noted in an excel sheet and the results were statistically analyzed using Stata software 12.1. All the groups were compared using one-way analysis of variance and multiple comparisons between the groups were performed with Bonferroni correction.

Results

Demography

A total of 98 eyes from 49 patients were included in the final assessment. The mean age in group 1 was 16.1 ± 1.85, 24.7 ± 3.19 in group 2, 35.3 ± 3.40 in group 3, 46.5 ± 2.59 in group 4 and 55.88 ± 2.02 in group 5. There were 10 subjects each in groups 1, 2, 3, and 4, whereas group 5 had only 9 subjects for the final assessment. The male to female ratio was 1.5:1 in group 1, 0.66:1 in group 2, 2.33:1 in group 3, 1.5:1 in group 4 and 1.2:1 in group 5.

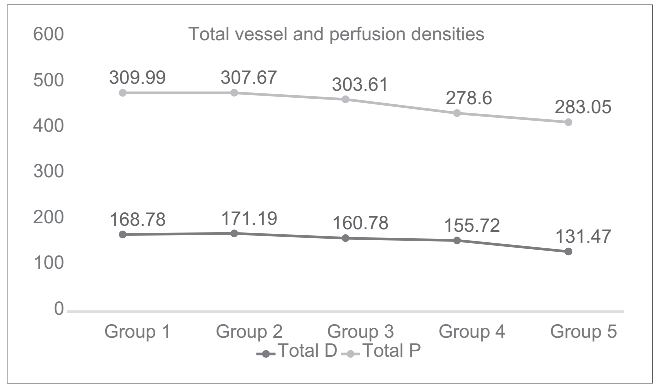
Vessel density changes

Total VD (all four quadrants of both the eyes) showed a slight increase in group two (171.19 ± 8.03) as compared with group 1 (168.78 ± 10.02) (not statistically significant, $P > 0.05$), followed by a gradual decline from group 3 to group 5. However, the reduction in total vessel density values reached statistical significance only in group 5 as compared with group 1 (131.47 ± 18.32, $P = 0.000$) [Graph 1]. Intergroup comparison between group 1 to 2, group 1 to 3, and group 1 to 4 was also performed however, these were not statistically significant [Graph 1].

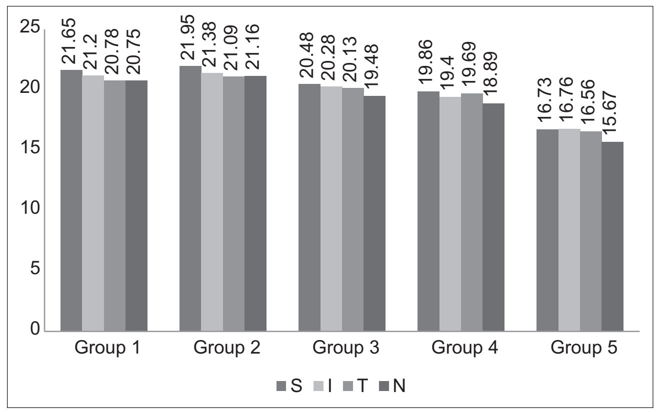
Similarly, on separate quadrant-wise (superior, inferior, nasal and temporal) analysis, the mean VDs along each quadrant were slightly lower in group 1 as compared with group 2, but this was not statistically significant (all quadrant $P > 0.05$). In contrast, the VD along each quadrant showed a decline in groups 3, 4, and 5 when compared with group 1. On comparing with group 1 (superior –21.65 ± 1.50, inferior –21.2 ± 1.53, temporal –20.78 ± 1.78, and nasal –20.75 ± 1.28), the fall in quadrantic vascular density reached a statistical significance ($P < 0.05$) along the superior and inferior quadrants in group 4 (superior –19.86 ± 1.88, $P = 0.012$, inferior –19.40 ± 1.65, $P = 0.023$); and in group 5 (superior – 16.73 ± 2.28, $P = 0.000$, inferior –16.76 ± 2.29, $P = 0.000$); and also, along the nasal and temporal quadrants in group 5 (nasal –15.67 ± 3.04, $P = 0.000$, temporal –16.56 ± 2.63, $P = 0.000$) only. The entire data is presented in Table 1 and Graph 2. [Fig. 1, Table 1, Graphs 2-4].

Perfusion density changes

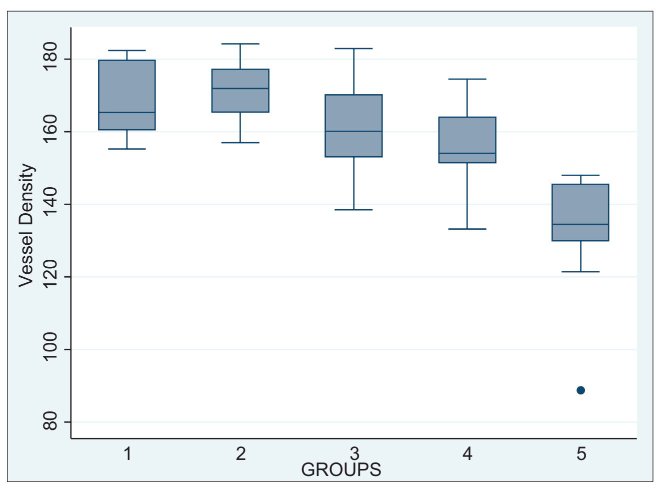
The total PD (all four quadrants of both the eyes) decreased with increasing age, but the reduction was not statistically significant ($P > 0.05$) [Graph 1]. The quadrant-wise assessment showed a reductionwithout any definite pattern although along some quadrants, P -value was significant. The entire data has been presented in Graphs 5-7 and Table 1 [Fig. 2].



Graph 1: Shows the total vessel and perfusion densities. Considering group 1 as a baseline, the *P* values for the total vessel densities after comparison with group 2, 3, 4, and 5 were 1.00, 1.00, 0.24, and 0.00, respectively. Similarly, the *P* values for group 2, 3, 4, and 5 were 1.00, 1.00, 0.086, and 0.264, respectively for perfusion densities



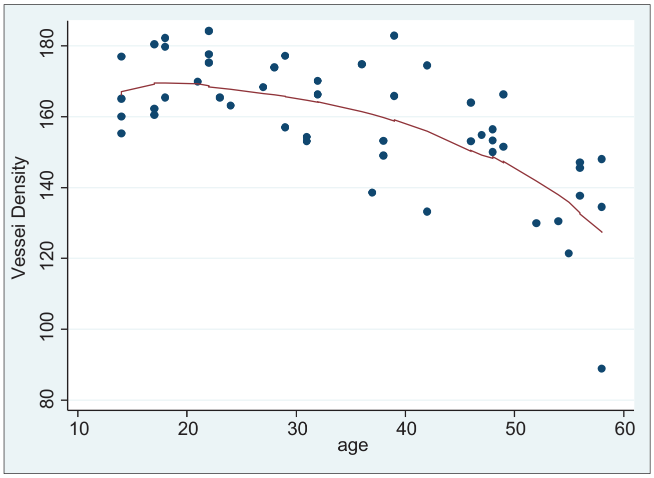
Graph 2: Shows the vessel densities along four quadrants in all 5 groups with increasing age. (S-superior, I-inferior, T-temporal, N-nasal)



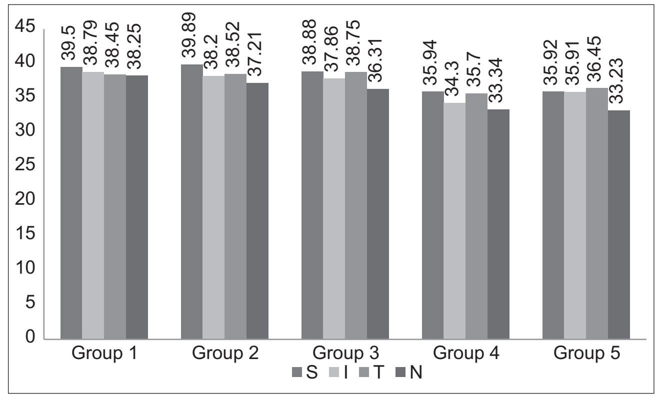
Graph 3: Showing Box and Wishker plot for total vessel density changes from group 1 to 5

Foveal avascular zone

The foveal avascular zone area (FAZ) was smallest in group 1 (0.18 ± 0.09 mm²). It increased to 0.33 ± 0.13 mm² in group 2, 0.30 ± 0.13 mm² in group 3, 0.38 ± 0.05 mm² and 0.46 ± 0.06 mm² in



Graph 4: Showing Scatter plot with Lowess curve for total vessel density changes revealing a linear decrease in vessel density with age



Graph 5: Perfusion densities along four quadrants in all 4 groups with increasing age. (S-superior, I-inferior, T-temporal, N-nasal)

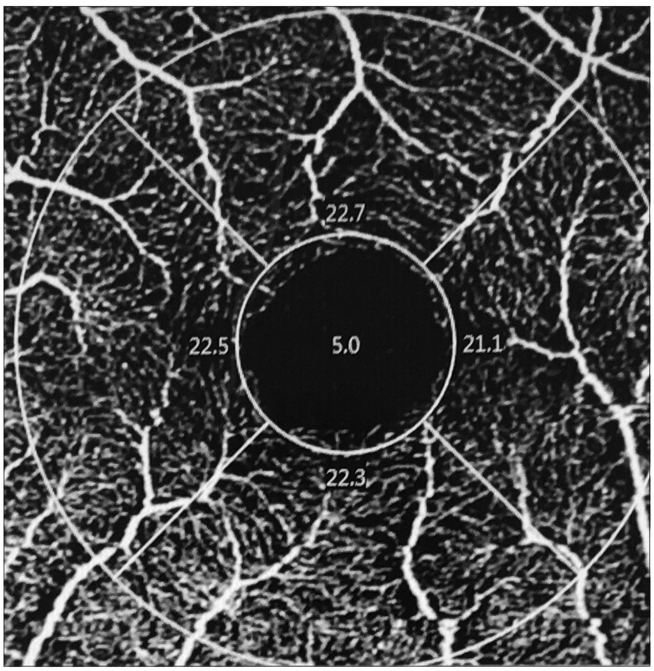


Figure 1: Automated values of vascular densities along superior, inferior, temporal, and nasal quadrants

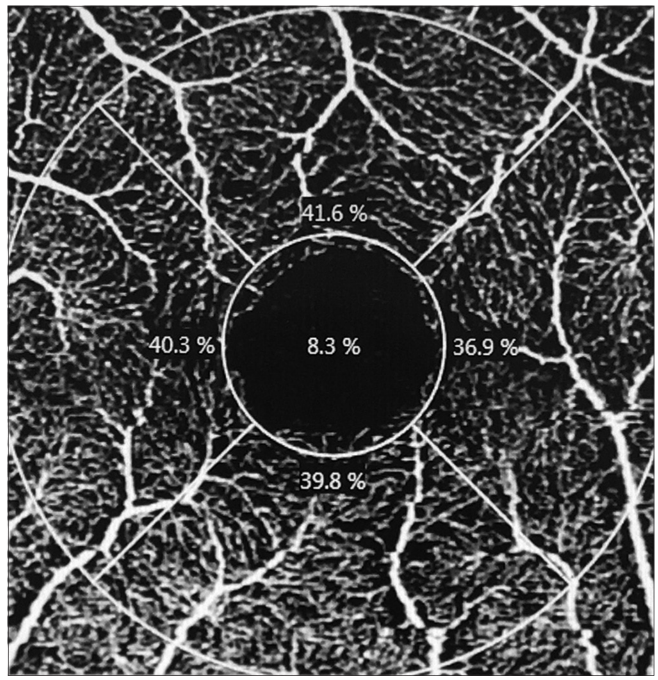


Figure 2: Automated perfusion density values along the superior, inferior, temporal, and nasal quadrants

group 4 and 5. This increase in size was statistically significant ($P = 0.00$) from group 2 onwards. [Table 2; Graphs 8 and 9]

The assessment of change in total vessel density each year using linear regression analysis revealed a coefficient of 3.71±0.27 at 95 % confidence interval. Similarly, the coefficient values for total perfusion densities and FAZ were 7.09±0.47 and 0.008±0.0002 at 95% confidence interval respectively.

Discussion

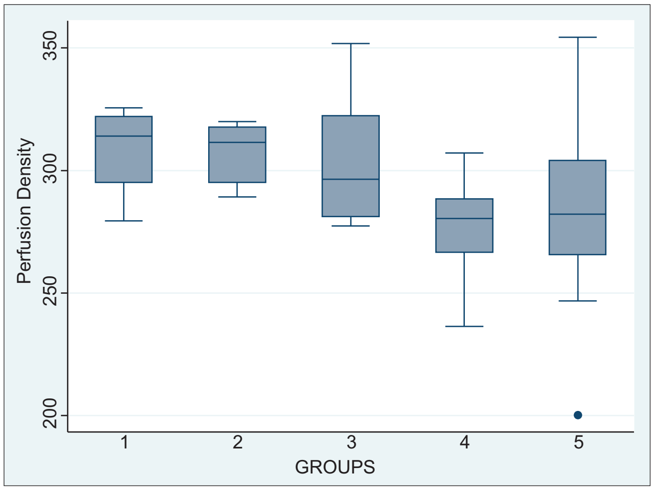
We evaluated perfusion density (PD), vessel density (VD), and FAZ in our population. Recently, after the introduction of OCTA in clinical use, various observational studies have been conducted to analyze the vascular network alteration in various diseases. These studies have noted variable changes in comparison to a certain set of controls but a definite comparison with respect to age-related changes may also be necessary, however, there is a scarcity of normative data within different geographical regions and races. Therefore, in this observation, we discuss the age-related changes in macular vessels and their PD along with foveal avascular zone dimension in the normal Indian population.

In our study, we mainly focused on the superficial plexus VDs and perfusion parameters, these values were drawn from an automated algorithm within the OCTA provided by the manufacturers. In simple terms, the PD is defined as the total area occupied by the vessels (considered as white pixels) divided by the total image area (black and white pixels) and the VD is the vessel length per unit area.

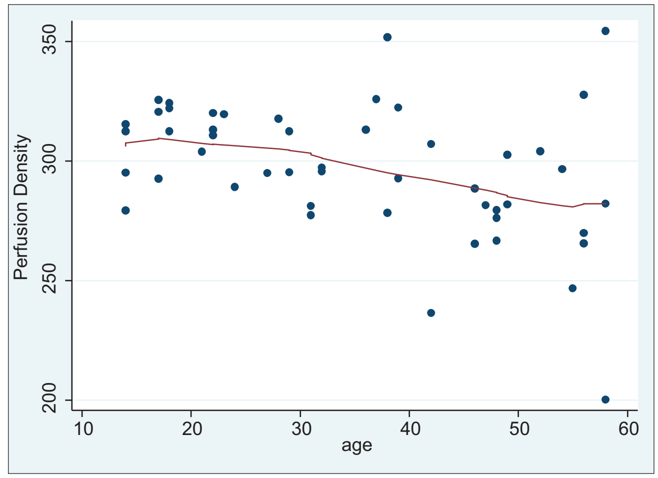
We noticed that the VDs were maximum in the second and third decades of life. For convenience and uniformity, we considered the second-decade values as optimal for comparison with the other groups and to observe the trend. Statistical analysis of the density values showed no significant changes

Table 1: Vessel and perfusion densities along the four quadrants in all 5 groups. The *P* values are mentioned after comparison between groups 1 to 2, groups 1 to 3, groups 1 to 4, and groups 1 to 5, respectively. The same has been mentioned for all quadrants of vessel and perfusion densities

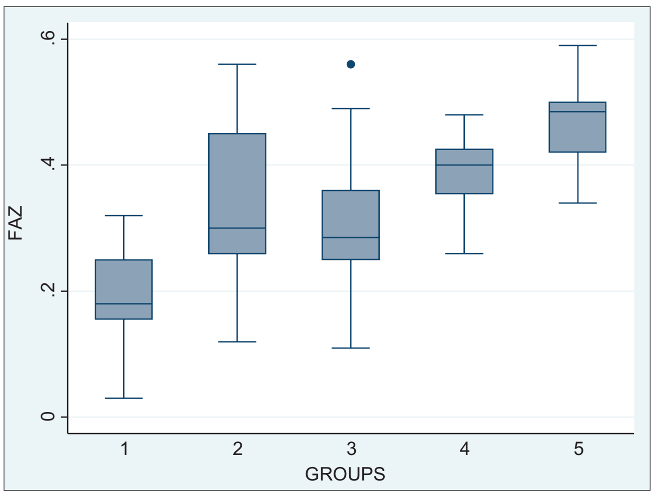
Groups	Age	Superior vessel density	Inferior vessel density	Temporal vessel density	Nasal vessel density	Superior perfusion density	Inferior perfusion density	Temporal perfusion density	Nasal perfusion density
1 (*n*=20 eyes)	16.1±1.85 Median 17 Min 14 Max 18	21.65±1.50 Median 21.7 Min 18.5 Max 24.3	21.2±1.53 Median 20.75 Min 19.5 Max 24.1	20.78±1.78 Median 20.8 Min 18 Max 24	20.75±1.28 Median 20.6 Min 18.2 Max 24.3	39.50±2.68 Median 39.85 Min 33.3 Max 44.3	38.79±2.54 Median 39.5 Min 34.1 Max 42.6	38.45±2.96 Median 39 Min 31.9 Max 44.9	38.25±3.12 Median 37.5 Min 33.5 Max 44.2
2 (*n*=20 eyes)	24.7±3.19 Median 23.5 Min 21 Max 29	21.95±0.97 Median 22.2 Min 20 Max 23.3 (*P*=1.00)	21.38±1.49 Median 21.4 Min 19.1 Max 24 (*P*=1.00)	21.09±1.40 Median 21.3 Min 18.3 Max 23.5 (*P*=1.00)	21.16±1.84 Median 21.3 Min 15.2 Max 23.5 (*P*=1.00)	39.89±1.69 Median 39.9 Min 36.1 Max 42.8 (*P*=1.00)	38.20±2.21 Median 39.05 Min 33.3 Max 41.2 (*P*=1.00)	38.52±2.58 Median 38.85 Min 32 Max 42.9 (*P*=1.00)	37.21±3.91 Median 38.1 Min 26.9 Max 41.5 (*P*=1.00)
3 (*n*=20 eyes)	35±3.40 Median 36.5 Min 31 Max 39	20.48±1.59 Median 20.75 Min 17.7 Max 23.4 (*P*=0.312)	20.28±1.99 Median 20.35 Min 17 Max 23.3 (*P*=1.00)	20.13±1.74 Median 20.35 Min 17 Max 23.4 (*P*=1.00)	19.48±2.49 Median 20.05 Min 13.6 Max 22.9 (*P*=0.74)	38.88±3.36 Median 38.65 Min 34.6 Max 46.2 (*P*=1.00)	37.86±3.18 Median 38.05 Min 32.2 Max 43.5 (*P*=1.00)	38.75±3.02 Median 38.5 Min 32.2 Max 45.8 (*P*=1.00)	36.31±4.93 Median 36.75 Min 22.6 Max 45.6 (*P*=1.00)
4 (*n*=20 eyes)	46.5±2.59 Median 47.5 Min 42 Max 49	19.86±1.88 Median 20.1 Min 13.6 Max 23.1 (*P*=0.012)	19.40±1.65 Median 18.95 Min 17 Max 23.2 (*P*=0.023)	19.65±1.44 Median 19.85 Min 15 Max 21.7 (*P*=0.63)	18.89±2.13 Median 18.55 Min 13.2 Max 23.6 (*P*=0.09)	35.94±3.25 Median 36.5 Min 24.3 Max 40.5 (*P*=0.01)	34.30±2.96 Median 33.45 Min 29.8 Max 40 (*P*=0.00)	35.7±2.71 Median 36.75 Min 29 Max 39.3 (*P*=0.20)	33.34±4.53 Median 33.6 Min 21.9 Max 42.9 (*P*=0.01)
5 (*n*=20 eyes)	55.88±2.02 Median 56 Min 52 Max 58	16.73±2.28 Median 16.95 Min 11.8 Max 21.7 (*P*=0.00)	16.76±2.29 Median 17.2 Min 10.5 Max 19.9 (*P*=0.00)	16.56±2.63 Median 17.1 Min 11.5 Max 20.8 (*P*=0.00)	15.67±3.04 Median 15.9 Min 7.5 Max 21.2 (*P*=0.00)	35.92±5.34 Median 36 Min 26.3 Max 45.7 (*P*=0.01)	35.91±6.12 Median 36.3 Min 23.7 Max 45.3 (*P*=0.16)	36.45±6.21 Median 36.7 Min 25.6 Max 45.4 (*P*=0.98)	33.23±6.55 Median 34.2 Min 16.2 Max 42.9 (*P*=0.01)
Average	35.28±28±14.57 Median 36 Min 14 Max 58	20.20±2.46 Median 20.6 Min 11.8 Max 24.3	19.87±2.41 Median 19.9 Min 10.5 Max 24.1	19.71±2.39 Median 20 Min 11.5 Max 24	19.26±2.89 Median 19.95 Min 7.5 Max 24.3	38.07±3.78 Median 38.5 Min 24.3 Max 46.2	37.03±3.91 Median 38.05 Min 23.7 Max 45.3	37.59±3.82 Median 37.75 Min 25.6 Max 45.8	35.72±5.03 Median 36.4 Min 16.3 Max 45.6



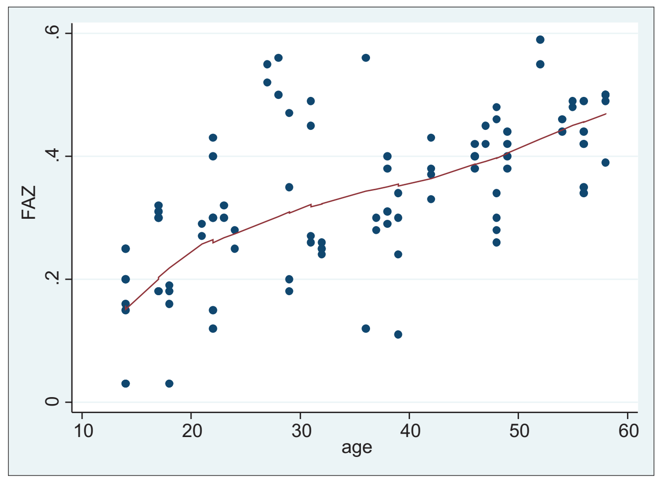
Graph 6: Showing Box and Wishker plot for total perfusion densities changes from group 1 to 5



Graph 7: Showing Scatter plot with Lowess curve for total perfusion density changes revealing a linear decrease in perfusion densities with age



Graph 8: Showing Box and Wishker plot for FAZ changes in group 1 to 5



Graph 9: Showing Scatter plot with Lowess curve for FAZ revealing a linear increase FAZ area with increasing age

Table 2: The FAZ area in mm^2 among 5 groups. The *P* values are mentioned after comparison between groups 1 to 2, groups 1 to 3, groups 1 to 4, groups 1 to 5, respectively

Groups	FAZ
1	0.18±0.09 (Median 0.18, Min 0.03, Max 0.32)
2	0.33±0.13 (Median 0.3, Min 0.12, Max 0.56) (*P*=0.00)
3	0.30±0.10 (Median 0.28, Min 0.11, Max 0.56) (*P*=0.00)
4	0.38±0.05 (Median 0.4, Min 0.26, Max 0.48) (*P*=0.00)
5	0.46±0.06 (Median 0.48, Min 0.34, Max 0.59) (*P*=0.00)

in any of the quadrants in the third and fourth decades with respect to the second decade, but from the fifth decade onwards there was a statistically significant decrease in density values were noted. However, the reduction became drastic along all the quadrants in sixth decade when compared with the second, third, fourth, and fifth decades. Similarly, the PDs also showed a trend of progressive reduction in percentage values with each decade, but these neither followed any definite pattern nor were they of statistical significance.

Previously, Iafeet *et al*. studied the age-related decrease in macular VD from first to eight decades in a total of 113 normal eyes. In their observation, superficial capillary plexus (SCP) vessel density was 13.431 ± 1.758 and deep capillary plexus (DCP) density was 18.812 ± 1.796. The density decreased at a rate of 0.0393 mm^{-1} (0.26% per year) along SCP and 0.0574 mm^{-1} (0.27% per year) along DCP per year. In accordance with this, they noted an average annual increase in the foveal avascular zone area of 0.0014 mm^2 along SCP and 0.0011 mm^2 along DCP.[1] In our study, the density was almost similar in the second and third decades but started to decrease from the fourth decade onwards. In the study by Iafeet *et al*., the VDs along the SCP were lower as compared with our values even in young patients; the reason for this is unknown, but this mandates age-related normative data in different populations so as to possess standardized values of that particular region/race.[1] Additionally, the measurements performed by them were on a different imaging platform. Thus, it might not be accurate to compare the values of OCTA machines from different manufacturers.

In another observation by Hassan *et al*., the flow densities along superficial and deep plexuses were comparable to our data, especially in the second and third decades.[2] These authors only assessed individuals in the third decade and did not report any age-related comparisons.[2] In addition, the findings of age-related decrease in the VDs,[3-5] radial peripapillary capillaries,[6] and increase in the FAZ[7] has been observed in different subjects with different ethnic groups but the pattern does not appear to follow a common trend. This could be due to several factors including different algorithms used for the quantification and racial factors, and due to other lesser-known facts about OCTA.

In both of the above observations, the DCP values were higher as compared with SCP. However, whether this is due to an actual increase in VD and flow along the deeper layers or due to projection artifacts needs further clarification. As the default software of the OCTA machine used by us does not provide quantitative data of the DCP, it was not studied by us.

Our observations of the drastic reduction in perfusion density (PD) and vessel density (VD) after fifth decade corroborates with the observations of Grunwald *et al*., where the authors noted significantly lower velocities and densities in subjects between sixth to eigth decades as compared to younger population.[8] However, we did not study individuals beyond the sixth decade.

Limitations of our study include a relatively small number of cases per group and we only evaluated the superficial capillary network using the inbuilt software. In addition, extremes of age were not included in our study and the results are only valid for the equipment we used. Different companies provide their own proprietary quantitative analysis software which may not corroborate with each other.

Conclusion

To conclude, the superficial retinal VDs and PDs were maximum in the second and third decades, whereas these values showed a decline thereafter. Although the VDs showed a fall from the fourth decade onwards, a statistically significant fall was noted only from the fifth decade. In contrast toVDs, the PDs did not show a statistically significant fall with increasing age. The FAZ area was smallest in the second decade, which showed a statistically significant increase in area from the third decade onwards and remained almost stable till the fifth decade. These normative standardized values of different age groups would be useful for future studies in the Indian population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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